Modeling and simulation of tumor growth

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***Abstract*—Mathematical Oncology has emerged as a dynamic research field that applies either continuous or discrete models to mathematically describe cancer-related phenomena. Such methods are usually expressed in terms of differential equations, however tumor composition involves specific cellular structure and can demonstrate probabilistic nature, often requiring tailor-made approaches. This study introduces three complementary strategies– agent-based modeling, system dynamics modeling and cellular automata– to capture the dynamics of tumor cell and normal cells' populations, incorporating the effects of chemotherapy. While agent-based and cellular automaton models offer microscopic insights, system dynamics modeling provides a macroscopic perspective. Results from all three models are synthesized, showcasing their collective contributions to our understanding of tumor growth dynamics. The integration of system dynamics modeling enriches the broader context, enhancing the overall robustness of our approach.**

The proposed models(Agent based model , cellular automata model and system dynamic model) are able to effectively simulate different scenarios regarding tumor growth effectively, figuring as an interesting tool for in silico modeling. With the incorporation of chemotherapy effects, these models demonstrate promising capabilities for expanding research in mathematical oncology, thereby contributing to the improvement of diagnostic tools and personalized treatment strategies.

I. Introduction

Tumor is classified into 3 classes: benign, premalignant, and malignant If someone has a malignant tumor, it is cancerous. Other types of tumor are not cancerous.

Cancer is the generic term attributed to a large group of diseases involving cells that develop characteristics allowing them to abnormally reproduce, progressively invading other tissues and unleashing several problems to the host . Also called malignant tumors or neoplasms, it caused almost 10 million deaths only in 2020, indirectly being responsible for an annual cost reaching trillion dollar figures. Although cancers have different adaptation and growth mechanisms depending on their origin in the body, they have similar traits and common genetic characteristics, generally arising from a single cancerous cell.

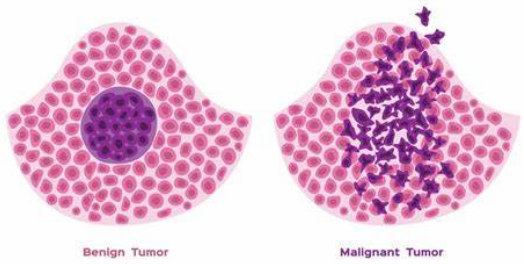

Fig. 1. bengin and premlignant tumors.

There are many methods to remove the tumor as surgery , phototherapy ,chemotherapy and others. We have chosen to simulate the chemotherapy treatment and how it work to kill the tumor.

Chemotherapy is a type of cancer treatment that uses chemicals called antitumors these chemicals may destroy the DNA of the tumor cell and prevent it from cellular division (the tumor die). [1]

This type of treatment has its pros and cons, Some of its pros that chemotherapy may shrink the cancer enough to make surgery to remove the cancer possible or it may help you to live longer and help with your symptoms, and one of its cons is that it may leave one or more tumor cells that can then be activated to generate new cluster of tumor cells, It affects everyone differently and may not work so well for some people. [3]

In our project we made 3 models to show the growth of the tumor and how chemotherapy can affect it. Each model has two type the real model and refinement model.

First, we used cellular automata because it can show a map for what happen to the tumor and natural cells from the begining of the tumor till its death after chemotherapy treatment.

Then, We used agent based diagram to show the interaction between the natural cells , tumer cells and chemotherapy medicine in more details.

Finally, we used system dynamic models to represent our equations and show on the long run what is going to happen to both tumor and natural cells after introducing the body to chemotherapy

II. Literature review

Over the last few decades , there have been significant development in understanding the dynamics of cancer cells and there interaction in immune system. These developments are important for cancer therapy including virotherapy, immunotherapy, chemotherapy, targeted drug therapy, and many other type of therapies. there have also been some developments on analytical and computational models which are capable of integrating biochemical factors and biophysical processes to simulate and predict cancer progression.

As mentioned in the introduction we choose to simulate the tumor growth and the effect of chemotherapy on the tumor cells.

in the previous researches they were curious to show the life of tumor through only one model usually cellular automata.

One of these researches use hybrid cellular automata modeling that reveals the effect of glucose gradients on tumor spheroid growth. It was published in 2023 Nov 30 [2]

its purpose was to use mathematical models to encompass diverse biological and physical process whisc are increasingly used in clinical setting showing predictive precision for individual patient outcomes and therapeutic responses

its methods: the study use silico model for simulating tumor growth .The automated hybrid cell emulates critical tumor cell characteristics, including rapid proliferation ,motility ,reduced cell adhesion and responsiveness to chemotactic signals. This model explores the potential evolution of 3d tumor spheroids focusing on nutrient availability.

Its results: the tumor cells depend primarily on the speed of cell duplication and cell to cell adhesion , rather than external chemical gradients.On the other hand, chemotaxis is primarily responsible for tumour invasiveness. These revelations shed light on the processes behind tumour formation and offer crucial direction for developing tactics that impede the spread of tumours. Our suggested model is a useful resource for investigating possible treatment strategies and expanding the field of cancer biology research.

many other researches tried to use different many different models as agent based model ,system dynamic model and others .so, in our research models we tried to simulate the growth of tumor depending on the results of these published papers and we used the the three models (system dynamics model, cellular automata and agent based model) .

III. Models

A. cellular automata

Mathematical Oncology often employs various models to capture the intricate dynamics of tumor growth. In this study, we utilize a Stochastic Cellular Automaton (SCA) as a modeling approach. SCAs, are spatially and temporally discrete systems that introduce stochastic elements into traditional cellular automata. In an SCA, each cell's evolution involves probabilistic transitions, allowing for a more nuanced representation of tumor dynamics. Incorprating chemotherapy effects on tumor growth can contribute to improvements in personalized medicine by finding optimal dosages with least harm and cost. [4]

1) Assumptions: Several simplifying assumptions are made in our model to facilitate a clearer understanding of the core dynamics involved in tumor growth. These assumptions guide the construction of the Stochastic Cellular Automaton (SCA) and shape the scope of our simulation. The following assumptions have been considered:

1) Only tumor cells are taken into consideration, and the model does not distinguish between different subtypes of tumor cells (e.g., stem tumor cells).
2) Vascular growth around the tumor and the associated nutrient supply for the tumor are not considered in our simulation.
3) The model does not account for immune responses against the tumor, simplifying the focus to intrinsic tumor dynamics.

These assumptions allow for a focused exploration of the basic stochastic processes governing tumor evolution, providing insights into fundamental aspects of tumor behavior. It is essential to acknowledge these simplifications and recognize their impact on the interpretability and applicability of the simulation results.

2) Lattice Structure: In this section, we employ a probabilistic two-dimensional (L×L) Cellular Automaton (CA) model, representing a square lattice that mimics a tissue sample for simplicity. The lattice serves as the spatial framework for our simulation, where each site (i, j) is characterized by a state variable S(i,j).

The variable $S_{i,j}$ can take on the following values:

- 0: Normal living cell
- 2: Tumor cell
- 3: Dead tumor cell
- 4: Dead living cell

3) Stochastic Dynamics: Our CA model introduces stochastic elements, making it a Stochastic Cellular Automaton (SCA). The dynamics of the system are influenced by probabilities, reflecting the inherent randomness in biological processes. Random probabilities used in our model: tumor growth probability, tumor death probability, normal living death probability, dead cell regeneration probability

4) Neighborhood Configuration: To capture the local interactions within the lattice, we employ the Moore neighborhood. The neighborhood defines the set of neighboring cells considered when determining the next state of a given cell. Our model has a stochastic nature, where next states depend on probabilities and random number generation, however the neighbors of the cell also affects its next state, for a normal living cell the number of tumor cell neighbors affect its next state.

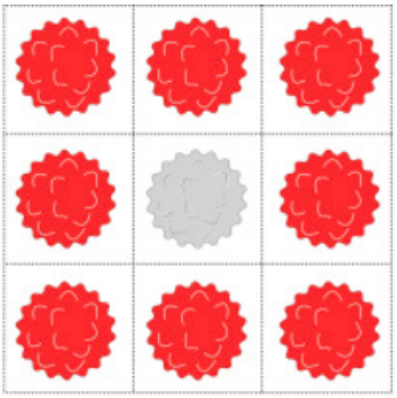

Fig. 2. Moore Neighbourhood Configuration

5) Transition rules: Our cellular automata model incorporates a dynamic transition rule to simulate the evolution of tumor cells in a two-dimensional grid. The transition rule governs the state changes of each cell at every iteration, contributing to the emergent behavior of the simulated tumor environment. It depends on probabilities and random number generation, inaddition, to the influence of neighbours which simulates tumor growth.

a) Tumor Cell Dynamics: For cells identified as tumor cells, the transition is influenced by stochastic events:

- **Tumor Cell Death:** Tumor cells have a probability of transitioning to a dead tumor cell, introducing randomness into the model to account for the unpredictable nature of cell death.

b) Normal Living Cell Dynamics: Cells initially in a normal living state undergo changes based on the state of their neighbors:

- **Neighbor Influence:** The model assesses the number of neighboring cells in the tumor state, capturing the local environment's impact on cell behavior.
- **Probability of Tumor Growth:** The probability of a normal living cell transitioning to a tumor cell is influenced by the count of neighboring tumor cells. A mapped probability is computed, adjusting the probability based on local conditions.
- **Living Cell Death:** In the absence of nearby tumor cells the probability of tumor growth remains the same. Inaddition, a normal living cell has a probability of transitioning to a dead living cell, modeling the natural death of cells.

c) Dead Cell Dynamics: Cells in a dead tumor or dead living state have the potential for regeneration:

- **Regeneration:** Dead cells exhibit a probability of regeneration, leading to a transition back to an empty space. This accounts for the potential renewal of the cellular environment.

The combination of these rules captures the stochastic and dynamic nature of cellular interactions within the simulated tumor environment, contributing to the overall realism and complexity of the model.

6) Monte Carlo Simulation: To enhance the robustness of our model and gain insights into its behavior under different conditions, we conducted a Monte Carlo simulation involving multiple independent runs. Each run represents a unique instantiation of the stochastic processes within the model, providing a diverse set of outcomes.

7) Simulation Procedure: We performed a series of N independent runs of our Stochastic Cellular Automaton (SCA) model, where each run initiates with a distinct random configuration of cells. The simulation captures the evolving dynamics of the tumor environment over a predefined number of generations.

8) Results and Analysis: The outcomes of the Monte Carlo simulation offer a comprehensive perspective on the variability of the model. Statistical analysis was applied to interpret the results, focusing on key metrics related to tumor growth across multiple runs.

a) Tumor Cell Count: The primary metric of interest is the final count of tumor cells at the end of each simulation run. The Monte Carlo results exhibit a distribution of tumor cell counts, enabling the computation of statistical measures such as mean and standard deviation.

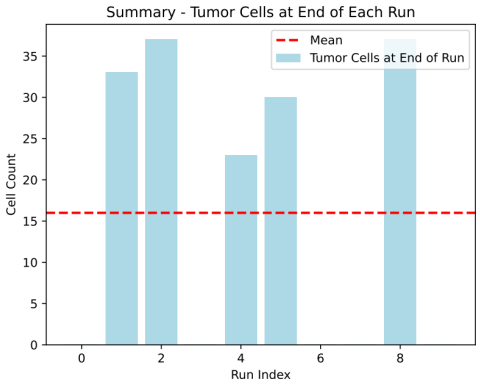

Fig. 3. Monte Carlo Simulation Results - Tumor Cell Counts

b) Mean and Standard Deviation: The mean and standard deviation of the tumor cell counts across multiple runs provide valuable insights into the central tendency and variability of the model outcomes. These measures contribute to a more comprehensive understanding of the stochastic nature of the tumor growth process.

9) Implications for Personalized Medicine: The Monte Carlo simulation results pave the way for personalized medicine applications. By exploring a range of potential scenarios, our model can assist in identifying optimal chemotherapy dosages that minimize harm and cost. The insights gained from the simulations contribute to the ongoing efforts in tailoring medical treatments to individual patient characteristics.

B. Agent Based Model

Agent-based modeling provides a dynamic and individualized framework for simulating tumor growth, allowing researchers to analyze the emerging behaviors and interactions of individual cells in a simulated environment, providing insights into cancer development's complexity and heterogeneity.

The tool we used for the agent based model is Netlogo, which allows us to represent each agent and track it. We started the model's representation by simulating the healthy cells, including their movement and death rate. We designed 3 shapes of healthy cells to aviod uniformity. After representing the normal, we started representing the tumor growth, with 2 different tumor shapes.

Tumor cells move, grows, and starts spreading with set probability to move , and probability to grow . We added a button "Kill Tumor" that represents the start of chemotherapy dose intake which will start to kill both normal and tumor cells but the tumorous cells will be killed by a higher rate because they intake more blood for glucose which is represented by probability to kill.

This model clarifies the cellular-level dynamics of tumor formation and growth. The simulated administration of chemotherapy investigates its effect on both tumorous and normal cells, adding to our understanding of the complex interplay at the cellular level in tumor treatment.

1) Assumptions:

- **Healthy Cells:**
  - **No new cells regenerated:** healthy cells number is constant, unless killed by chemotherapy, but no new cells.
  - **Healthy Cell Death:** healthy cells only die from chemotherapy.
- **Tumor Cells:**
  - **No immune response:** tumor cells will not be killed without chemotherapy.
  - **Kill Tumor:** Chemotherapy kills tumor based on set probability to kill, which represents amount of chemotherapy and body response in real life.
  - **Tumor Growth**: Tumor grow based on a set probability-to-grow which decreases when kill tumor is activated.
  - **Neighbour Cell:** Tumor grows into adjesecnt cells.
  - **Cell Imitation:** New tumor cell can grow and tumor cell can move.

2) Reinfinements:

- **Body Immunity:**
  Add effect of white blood cells t tumor death.
- **Reality-Probabilities Relation:**
  Add Relation between exact amount of chemotherapy, body immunity, body response and probabilities.
- **Response to Chemotherapy:**
  Visualize response of body to chemotherapy.
- **New Blood Vessel Generation:**
  Simulate blood vessel growth and new blood vessel creation based on tumor size to supply needed glucose for cells.

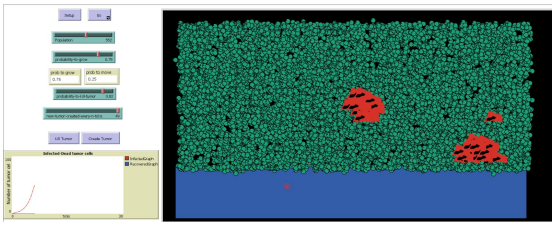

Fig. 4. Agent Based Model

C. system dynamics model

System dynamics one of easiest models that we can simulate and see how tumor expand and grow in human body maybe it is not realistic as agent based and CA model but its good start to observe the tumor growth before creating and implement more complex models.

*1) **Assumption**:* The following equation represents our assumption in SD model and here I explain it. Equation (1) we assumed that Normal cell has a capacity factor as we now population of normal cells has a limit. Also, normal cell can die normal death or can die by interacting with tumor cells. Equation (2) our assumption it has capacity factor that represent the limit that the organ can have of tumor cells. Also, tumor cells can die by normal death, interaction between immune cell and eliminated by Chemotherapy. Equation (3) human body contains many of kind of cells that can resist the tumor growth but for simplicity we assumed one cell that can resist tumor growth and we named it Immune cell.As well as Normal cell has a capacity Immune cell also has a capacity factor. Immune cell can be eliminated by normal death and interaction between it and tumor cell. Equation (4) Chemotherapy is taken on many courses but for simplicity we assumed that it is just one course or many courses represented in one huge course that has initial value and decay over time with out take another drug from start of simulation.

*2) **Differential Equation**:*

$$\frac{dN}{dt} = r_N N\left(1 - \frac{N+T}{K_N + 0.0001}\right) - d_1 N - iNT \quad (1)$$

$$\frac{dT}{dt} = r_T T\left(1 - \frac{N+T}{K_T + 0.0001}\right) - d_2 T - \beta IT - \alpha_1 CT \quad (2)$$

$$\frac{dI}{dt} = r_I I\left(1 - \frac{T+I}{K_I + 0.0001}\right) - d_3 I - \alpha_2 TI \quad (3)$$

$$\frac{dC}{dt} = -d_4 C \quad (4)$$

N: Normal cell population
T: Tumor cell population
I: Immune cell population
C: Chemo Concentration
r_N: Growth rate of normal cells
d_1: Normal death rate of normal cells
i: Interaction rate between normal and tumor cells
r_T: Growth rate of tumor cells
d_2: Normal death rate of tumor cells
β: Interaction rate between immune cells and tumor cells (tumor gets killed)
α_1: Rate at which tumor interacts with chemotherapy and gets killed
r_I: Growth rate of immune cells
d_3: Normal death rate of immune cells
α_2: Rate at which immune cells interact with tumor and get killed
d_4: Decay rate of chemotherapy inside the body
K_N: capacity factor of Normal cells
K_T: capacity factor of Tumor cells
K_I: capacity factor of Immune cells

*3) **SD model**:* the following figure shows our SD model and the follows between our assumed stocks

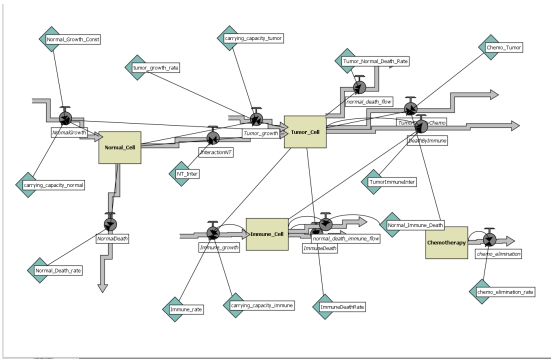

Fig. 5. SD for tumor growth

As for refinement we assumed tumor die only by immune cells and when interacting with tumor cells and we removed chemo stock where tumor just die by constant rate from Chemo constant without chemo Stock and die from interacting with immune cells.

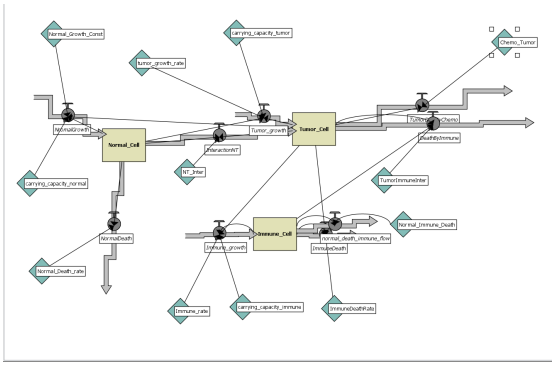

Fig. 6. refined SD for tumor growth

*4) **Numerical Solution**:* In this part we will show how we solved the model buy using Euler's method and Runge-Kutta 2 method. we assumed our constant values as follows N=100, T=10, I=50,C=100, r_N=0.05, d_1=0.019108, i=0.0001, r_T=0.2, d_2=0.019108, β= 0.0001, α_1=0.00526 r_I=0.08 ,d_3=0.00009, α_2=0.00526, d_4=0.2, K_N=1500, K_T=800, K_I=500

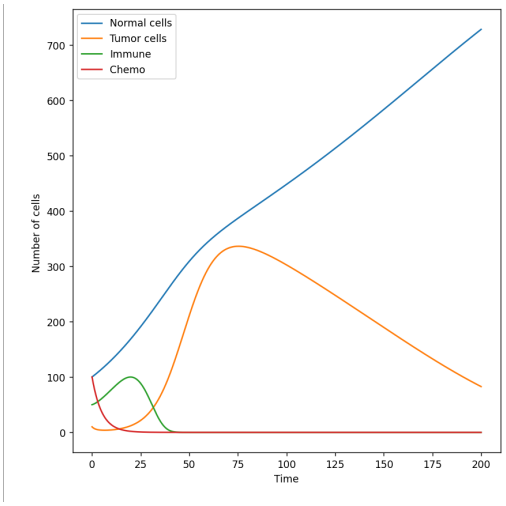

Fig. 7. tumor growth graph 1

IV. Refinements

To capture the complexity of tumour growth dynamics while maintaining computational feasibility and interpretability, our study makes use of multiple degrees of simplification. Achieving a balance between realism and model complexity requires these levels of simplification. The main layers of simplification that our modelling framework incorporates are outlined below:

1. **Macroscopic System Dynamics:** The System Dynamics model provides the fundamental macroscopic description by showing the general dynamics of immune cells, tumour cells, normal cells, and the effects of chemotherapy. A worldwide

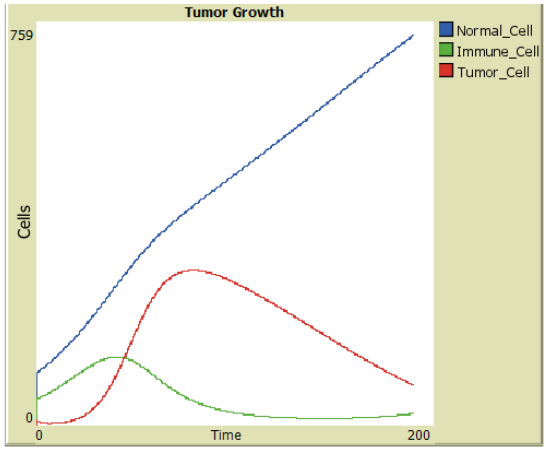

Fig. 8. tumor growth graph 2

understanding of the interactions within the tumour microenvironment is provided by this high-level abstraction.

2. **Cellular Automata Refinement:** The probability of a cell transforming into a tumor is considered constant but is dynamically adjusted based on the number of tumor neighbors. Tumor cell death is modeled as the sum of normal cell death, immune response, and chemotherapy, each treated as a constant but subject to dynamic changes using sliders. This approach enables the exploration of various scenarios by adjusting parameters in real-time, providing insights into the complex dynamics of tumor development and treatment outcomes. The model's flexibility offers a valuable tool for researchers to refine their understanding of cancer biology and optimize treatment strategies.

3. **Microscopic Agent-Based Modeling:** The Agent-Based Model investigates the stochastic behaviours of individual cells at the microscopic level. This method contributes to a thorough knowledge of emergent behaviours and variations in cell dynamics by taking into account the heterogeneity and unpredictability in cellular responses to external inputs. As for refinement we assumed tumor die only by immune cells and when interacting with tumor cells and we removed chemo stock where tumor just die by constant rate from Chemo constant without chemo Stock and die from interacting with immune cells.

We are able to achieve a compromise between preserving computational tractability and capturing crucial aspects of tumour growth thanks to these degrees of simplification. The incorporation of macroscopic, mesoscopic, and microscopic viewpoints amplifies our modelling framework's adaptability to various study inquiries and permits a multi-scale investigation of tumour dynamics.

Although each step of simplification adds certain abstractions, taken as a whole, they offer a flexible and thorough platform for examining the complex interactions that occur between chemotherapy, tumour cells, immune cells, and normal tissue inside the tumour microenvironment.

V. Future Work

Future research in the field of tumor growth modeling, particularly in the context of chemotherapy treatment, can build upon our existing Cellular Automata (CA) model, System Dynamics model, and Agent-Based Tumor model. Here are several avenues for further investigation:

- **Refinement of Chemotherapy Interaction:** Expand on the current model by investigating the ways in which chemotherapy interacts with tumour cells. To maximise therapeutic results and reduce possible side effects, experiment with various chemotherapy drugs, doses, and treatment regimens. For a more accurate depiction of the dynamics of chemotherapy, think about include pharmacokinetic and pharmacodynamic data.
- **Incorporation of Immune System Dynamics:** Extend the model to incorporate the immune system's dynamics in reaction to treatment and tumour growth. Examine the interactions between immune cells and tumour cells as well as the effects of chemotherapy on the immune system. This contribution would shed light on the intricate interactions that exist between the tumour, the immune system, and the course of treatment.
- **Simulation of Tumor Microenvironment Variability:** Extend the model to replicate the formation of tumours in various microenvironments that correspond to distinct tissue types or organ systems. Examine the ways in which differences in the tumour microenvironment affect the effectiveness of chemotherapy. This investigation may lead to a more thorough comprehension of how various biological settings affect the course of treatment.
- **Analysis of Resistance Mechanisms:** Examine possible ways in which tumour cells could become resistant to treatment. Examine how the tumour population's adaptive alterations or genetic mutations affect the response to treatment. Developing more individualised and efficient treatment plans can be aided by an understanding of resistance mechanisms.
- **Optimization of Treatment Strategies:** To determine the best chemotherapy regimens based on particular tumour features, conduct optimisation studies. Apply computational techniques to forecast and evaluate the efficacy of various treatment approaches, taking into account variables like medication regimens and dosage orders.

These recommendations seek to deepen our knowledge of the dynamics of tumour growth during chemotherapy and lay the groundwork for the creation of more individualised and efficient therapeutic modalities.

VI. Conclusion

As a result, our research delves into the complex dynamics of tumor growth and takes a holistic approach by combining three different models: System Dynamics, Cellular Automata, and Agent-Based Modelling. A comprehensive understanding of the relationships between tumour cells, immune system cells, and normal tissue as well as the effects of chemotherapy

on cellular dynamics was made possible by the combined use of these models.

The System Dynamics model provided the underlying structure, illustrating the basic connections between tumor, immune, and normal cells as well as the impact of chemotherapy. With the aid of this model, we were able to create a comprehensive understanding of the tumor growth process and get insight into the general dynamics controlling the system.

The Cellular Automata model provided a thorough analysis of the interactions between neighbouring normal cells to ascertain the likelihood of infection. We were able to record the local interactions that affect the beginning and development of tumour cells within the tissue thanks to this probabilistic method. Through the integration of microscale cellular behaviours, the Cellular Automata model improved our comprehension of the spatial dimensions involved in tumour formation.

The Agent-Based Model presented a stochastic viewpoint on the intricate mechanisms behind tumour formation by simulating the individual behaviour of cells using a random model. With the help of this model, we were able to investigate the diversity and emergent behaviours of individual cells, which helped to clarify the dynamic nature of how cells react to their surroundings.

When combined, these three models provided a synergistic description of the dynamics of tumour growth from both macroscopic and microscopic angles. Our investigation into the interactions among immune cells, tumour cells, and normal tissue, along with the evaluation of the effects of chemotherapy, contribute to our understanding of how cancer progresses and how treatments work.

The application of various modelling approaches not only enhanced our understanding of tumour growth but also cleared the path for additional research directions. By combining these models, a strong basis for investigating the complexities of cancer dynamics is created, which makes it easier to create individualised and targeted treatment plans.

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Dr. Rushdi's extensive knowledge and insightful feedback significantly contributed to the conceptualization and design of our model. His advice proved crucial in navigating the complexities of Tumor growth and treating it with chemotherapy while ensuring the model's accuracy and scientific rigor. The authors extend their sincere gratitude for Dr. Rushdi's mentorship and the dedicated time he invested in discussing and refining their ideas.

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